A Notice of Appeal with Petition for Extension of Time and a check for the appropriate fee were mailed to the Patent Office on March 29, 1999 for filing in the above-referenced application.

REMARKS

The Examiner's withdrawal of several of the rejections made in Paper No. 12 under 35 U.S.C. §§ 112, first and second paragraphs, including the deposit requirement, and the rejections under 35 U.S.C. §§ 102(b) and 103(a), is acknowledged with appreciation.

Rejection of Claims 14-15 and 36-37 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has maintained the rejection of Claims 14-15 and 36-37 under 35 U.S.C. § 112, second paragraph, alleging that it is "unclear whether 'cA2' represents a genus of chimeric antibodies or a species, a unique chimeric clone" and that "applicant's arguments and referenced portions of the specification do not clarify this issue." Applicants respectfully disagree that the term "cA2" is unclear.

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986). If the claims read in light of the specification reasonably appraise those skilled in the art of the scope of the invention, § 112 demands no more. Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1987), *cert. denied*, 480 U.S. 947 (1987).

As discussed in Amendment B, filed July 9, 1998, the specification teaches that cA2 designates a chimeric monoclonal antibody (i.e., a species) which is characterized by the antigen binding variable region of monoclonal antibody A2 and the constant regions of a human IgG1, κ immunoglobulin (see, e.g., page 12, lines 23-26; and page 16, lines 14-15 and 18-19). In addition, significant description of the properties of the monoclonal antibody cA2 (e.g., epitopic specificity and affinity) is disclosed in U.S. Application No. 08/192,102 (now U.S. Patent

No. 5,656,272; see, e.g., Examples X-XII therein) and U.S. Application No. 08/324,799 (now U.S. Patent No. 5,698,195; see, e.g., Examples X-XII therein), both incorporated by reference in Applicants' specification (see, e.g., page 12, lines 12-17). Additionally, the sequences of the antibody are described therein. Accordingly, when read in light of the specification, the metes and bounds of the claims can be determined by a person skilled in the art. That is, when read in light of the specification, a person skilled in the art would find the term "cA2" to be clear and definite.

Moreover, it is noted that the term "cA2" is recited in several of the claims of U.S. Patent No. 5,698,195 and U.S. Patent No. 5,656,272.

The Examiner has failed to identify any other portion of the specification which suggests that "cA2" refers to a genus of antibodies. The Examiner has also failed to explain why the definitions provided in this specification render the use of this term indefinite or otherwise unacceptable. It is noted that the burden is on the Patent Office to establish that the claim is indefinite. The Examiner is merely offering a conclusory assertion and has failed to meet this burden.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Rejection of Claims 6, 8-10, 12-15, 29-32 and 43-47 Under 35 U.S.C. § 112, First Paragraph

The rejection of Claims 6, 8-10, 12-15, 29-32 and 34-37 under 35 U.S.C. § 112, first paragraph, has been maintained on the grounds that the specification does not provide an enabling disclosure commensurate with the scope of the claims. The Examiner alleges that "one of skill in the art would not have a reasonable expectation of success, that anti-TNF antibodies would broadly 'prevent thrombosis' or 'decrease plasma fibrinogen', in any patient, irregardless of the etiology." With regard to Claims 6 and 29, the Examiner also maintains that it would require undue experimentation for one skilled in the art to practice the claimed invention using the many classes of molecules defined to be a TNF antagonist because the "[g]uidance for making and using this very broad collection of molecules can not be drawn from the making and using of

antibodies in the claimed method." Applicants respectfully disagree with the Examiner's assessment.

Claims 6, 8-10 and 12-15 relate to methods of treating or preventing thrombosis in an individual in need thereof comprising administering a therapeutically effective amount of a TNF antagonist to the individual. Claims 29-32 and 34-37 relate to methods of decreasing plasma fibrinogen in an individual suffering from or at risk of thrombosis comprising administering a therapeutically effective amount of a TNF antagonist to the individual.

To be enabling under 35 U.S.C. § 112, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). Further, "Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct." In re Armbruster, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975).

The specification teaches that thrombosis can be treated or prevented in an individual by administering a TNF antagonist to the individual in therapeutically effective amounts (see, e.g., page 6, lines 19-20). Examples of TNF antagonists are provided in the specification, for example, at page 7, line 9 to page 29, line 7. Guidelines for route of administration and dosages are provided in the specification, for example, at page 29, line 9 to page 32, line 4.

The specification discloses at page 4 that many patients with rheumatoid arthritis (RA) ultimately die from cardiovascular and cerebrovascular diseases (see page 4, lines 2-4). The specification also discloses that persistently elevated plasma fibrinogen and/or platelet levels are major contributors to the excess cardiovascular and cerebrovascular mortality seen in RA patients (see page 4, lines 4-9). See also Wolfe *et al.*, *Arthritis Rheum.*, 37:481-494 (1994); reference AT on Form PTO-1449.

The Examiner acknowledges that the specification teaches that the administration of anti-TNF antibodies to rheumatoid arthritis patients results in a decrease in elevated fibrinogen levels

to a range closer to normal and that inhibition of the biological activity of TNFα reduces fibrinogen and platelet levels in individuals with active rheumatoid arthritis (see, e.g., page 2, lines 14-18; page 5, lines 6-10; and page 36, Table 2 of the specification). Paper No. 15, at page 4, lines 14-18. Given these results, one skilled in the art on the effective filing date of the application would reasonably have expected anti-TNF antibodies to be effective in the treatment of thrombosis, particularly since fibrinogen and platelets play integral roles in thrombosis. That is, one skilled in the art would reasonably have expected that a means of decreasing fibrinogen levels would likely be effective in the treatment of thrombosis. No evidence to the contrary has been presented.

As defined in the specification, TNF antagonists decrease, block, inhibit, abrogate or interfere with TNF activity *in vivo* (see, e.g., page 7, lines 7-9). Applicants disclose that TNF antagonists include anti-TNF antibodies and receptor molecules which bind specifically to TNF, agents which prevent or inhibit TNF synthesis or TNF release, and agents which prevent or inhibit TNF receptor signaling (see specification, e.g., page 7, lines 9-25). Specific examples are provided as well (see specification, e.g., page 7, line 7 to page 17, line 9; page 26, line 29 to page 29, line 7). As evidenced by the art of record and the art cited in the specification, there are numerous TNFα antagonists known in the art. Other TNF antagonists can be identified using art-known screening methods.

Since anti-TNFα antibody antagonists function by antagonizing or otherwise inhibiting the activity of TNFα, one skilled in the art would reasonably expect that the claimed methods work in the same manner using other agents which antagonize TNFα. That is, one skilled in the art would accept the assertions in the specification as true and enabling. No evidence to the contrary has been presented.

Thus, Applicants respectfully submit that the guidance provided in the specification is sufficient to enable the skilled artisan to practice the full scope of claimed invention with a reasonable expectation of success and without undue experimentation.

The Examiner goes on to state in the rejection that:

> There is absolutely no evidence of record that outside of the context of the pathological state of rheumatoid arthritis, that anti-TNF antibodies influence

fibrinogen level and thrombosis. For example, the main presenting symptoms of rheumatoid arthritis are pain, stiffness, swelling and loss of function. Similar symptoms of rheumatoid arthritis are also the main presenting symptoms in another form of arthritis, osteoarthritis. However, from studies of model systems for both rheumatoid and osteoarthritis, it is art accepted that anti-TNF antibodies would have a modulatory effect in only rheumatoid arthritis and not osteoarthritis (see U.S. Patent 5,698,195 (col. 38, lines 46-55). Thus, anti-TNF antibodies do not broadly inhibit joint pain and stiffness, from all causes.

Applicants respectfully disagree with this assessment. It is believed that this argument is being relied upon as providing evidence that one skilled in the art would not readily accept that the specification provides enabling support for the claimed invention.

It is agreed that rheumatoid arthritis is a distinct disease, with unique pathological parameters that are known to be associated with an increased production of TNF. This, however, would not have led one of ordinary skill in the art to reasonably conclude that a means of decreasing a component which plays an integral role in thrombosis, i.e., fibrinogen levels, would not be effective in the treatment of thrombosis. No evidence to the contrary has been presented.

U.S. Patent No. 5,698,195 discloses in the passage referenced by the Examiner (i.e., at col. 38, lines 46-55) that, in evaluating whether TNFα is a suitable therapeutic target for the therapy of rheumatoid arthritis, the effects of anti-TNF antibody and peptides on rheumatoid joint cultures and osteoarthritic cell cultures were studied. The referenced passage reports that the anti-TNF antibody abolished IL-1 production, showing TNFα as a suitable therapeutic target for the therapy of rheumatoid arthritis, and refers to Brennan *et al.* (*Lancet, 11*:244-247 (1989); attached hereto as the Exhibit) (col. 38, lines 50-54).

The Brennan *et al.* reference reports the results of a study in which the effect of anti-TNF antibodies on synovial cell IL-1 production was investigated in 7 patients with rheumatoid arthritis and in 7 patients with osteoarthritis. Brennan *et al.* found that synovial cell IL-1 production was significantly reduced by anti-TNF antibody in cultures from patients with rheumatoid arthritis (see, e.g., page 246, Table II). In cultures from 6 of the 7 patients with osteoarthritis (i.e., patients 1, 2 and 4-7), Brennan *et al.* found that spontaneous IL-1 production was low despite high concentrations of TNFα (see, e.g., page 245, Table I; and page 254, col. 2,

** supports my argument

lines 17-25), and IL-1 production was not inhibited by anti-TNF antibody (see, e.g., page 246, Table II). In the culture from the remaining patient with osteoarthritis (i.e., patient 3), synovial cell IL-1 production was comparable to synovial cell IL-1 production in the rheumatoid arthritis cultures (see, e.g., page 245, Table I). In addition, similar to that found in cultures from patients with rheumatoid arthritis, synovial cell IL-1 production was inhibited by anti-TNF antibody in culture from this patient with osteoarthritis (i.e., patient 3) (see, e.g., page 246, Table II; and page 246, col. 1, lines 15-20).

These results are said to indicate that inhibition of IL-1 activity by anti-TNFα antibody in culture was only apparent with a high initial IL-1 concentration (Brennan *et al.*, sentence bridging pages 246 and 247). Thus, in osteoarthritis synovial cultures where the initial IL-1 concentration is low, anti-TNFα antibody would not be expected to inhibit IL-1 activity. However, in osteoarthritis synovial cultures where the initial IL-1 concentration is high, anti-TNFα antibody would be expected to inhibit IL-1 activity. Accordingly, Brennan *et al.* (and, as such, Le *et al.*) do not support the Examiner's assertion that "it is art accepted that anti-TNF antibodies would have a modulatory effect in only rheumatoid arthritis and not osteoarthritis". As such, Le *et al.* and Brennan *et al.* do not provide a sufficient basis to question the enablement provided in the disclosure for the claimed invention.

Thus, it is reasonable to conclude that, more likely than not, a person skilled in the art, viewing Applicants' teachings, the evidence provided in the specification, and the information known in the art at the time the subject application was filed, would still consider credible the teachings and results contained in the specification which are relied upon for enabling support of the claimed invention. That is, for the reasons discussed above, a person skilled in the art would have found the guidance provided in the specification to be sufficient to enable practice of the full scope of claimed invention with a reasonable expectation of success and without undue experimentation. The PTO has not explained why it doubts the truth or accuracy of the statements in the disclosure or provided evidence or reasoning which is inconsistent with the teachings of the disclosure. As discussed above, Le *et al.* and Brennan *et al.* do not provide a sufficient basis to question the enablement provided in the disclosure for the claimed invention.

Thus, there is nothing of record which might suggest that the claimed invention is not believable to one of skill in the art.

Reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Helen Lee

Helen Lee
Registration No. 39,270
Telephone: (781) 861-6240
Facsimile: (781) 861-9540

Lexington, Massachusetts 02421
Dated: April 21, 1995